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EQUATIONS FOR THE AGE STRUCTURE OF GROWING POPULATIONS

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Generalized equations are developed for the age structure of growing cell populations when other parameters besides chronological age are taken into account. These are summarized in a parameter which we call "chronological age." The theory is Markovian in spirit and leads to an integro-differential equation for population density which generalizes several equations now appearing in the literature. Approximations to the fundamental equation are suggested.

Introduction. Recent interest in a mathematical description of the age structure of growing cell populations has centered on the use of an equation proposed by von Foerster (cf. also Scherbaum and Rasch). This equation is a first order partial differential equation for a function $n(a, t)$ defined so that $n(a, t)\, da$ is the number of organisms at time t whose ages lie in the interval $(a, a + da)$. Properties of solutions to the von Foerster equation have been studied extensively by Trucco and by Nooney. Similar ideas are also contained in some work of Oldfield. The age a that appears as an independent variable in $n(a, t)$ is always interpreted as the chronological age of the organism. In consequence, the properties of two organisms belonging to a single age-cohort and subjected to identical environments are identical. Thus, the important feature of biological variability is omitted from the description of the age structure of a single cohort. This observation has been made and elaborated on by Stuart and Merkle in a discussion of cancer chemotherapy and by Rubinow in a study of hemopoeisis. A recent pair of studies by Bell, Anderson and Petersen has included cell volume as an additional variable determining population size.

The introduction of the volume parameter and a postulated growth rate allowed a fairly accurate description of observed volume distributions in cell culture lines as discussed in their papers. Tsuchiya, Frederickson, and collaborators have extensively developed the consequences of treating cell mass as an indicator of cell age, following the work of Koch and Schaechter, who introduced the idea.

It is the purpose of this paper to present Markovian equations which generalize those of von Foerster and of Bell and Anderson. These equations take into account the notion of a physiological age in addition to the chronological age. We therefore assume that there exists a variable, α, which is a state variable for the organism and will be called the physiological age. The property of α that will be used is that it can be assigned a numerical measure. For simplicity it will be assumed that α is a scalar quantity, although it is probable that a more accurate theory would require consideration of vector α. A precise interpretation of α will also be unspecified except to note that an analogous quantity appears in a theory of aging proposed by Sacher. The physiological age can also be identified with the number of chromosome faults as in the theory of Szilard, or with the "vitality" parameter appearing in a stochastic version* of the theory of Strehler and Mildvan. In Bell and Anderson's theory, the physiological age can be identified with cell volume. Tsuchiya and his coworkers have obtained similar results in their use of the cell mass as a state variable.

The theories mentioned above as well as that to be discussed in this paper can all be classed as Markovian. That is to say, growth and death rates depend on the state of the cell and time, but not on how long a cell has been in a given state. One might expect that a Markovian theory of growth would be inadequate for all but the simplest situations and that a more general theory including the time in given states would be required. Such a theory has indeed been developed and used in demography (see, for example, the references in Bartlett), but the resulting equations are very difficult to work with. However, a renewal process can sometimes be approximated by a Markov process provided that additional parameters are introduced to describe the system.

Kendall's model for bacterial growth is an illustration of this procedure. Our introduction of a new parameter (or set of parameters) therefore makes the resulting Markovian theory somewhat more plausible, although it cannot be construed as a justification for the theory.

Derivation of Equations. The chronological age of an organism will be

* Although the authors do not make the point explicitly, it is clear that the vitality they discuss is really a mean value and that fluctuations are possible.

denoted by a. The function of principal interest will be a number density to be denoted by $n(a, \alpha; t)$ and such that

$$\int_{a_1}^{a_2} da \int_{a_1}^{a_2} d\alpha\, n(a, \alpha; t)$$

is the total number of organisms between the chronological ages a_1 and a_2, and physiological ages α_1 and α_2. Thus the number density $n(a, t)$ appearing in von Foerster's treatment of the problem can be expressed in terms of $n(a, \alpha; t)$ as

$$n(a, t) = \int_0^\infty d\alpha\, n(a, \alpha; t). \tag{1}$$

Parenthetically we note that an even more detailed theory can be developed for a probability density $n_r(a, \alpha; t)$ defined such that $n_r(a, \alpha; t)\, da\, d\alpha$ is the probability that there are r individuals in the population and that each one of them has a chronological age between α and $d\alpha$. The distinction between a completely stochastic theory and one expressed in terms of number densities is unimportant when the functions specifying growth and death are independent of population size. Under these conditions it can be shown that the mean values derived from a stochastic theory satisfy the equations derived in this paper. This is not necessarily true for cell concentration dependence. The modifications required to develop a completely stochastic theory will be discussed elsewhere. The present paper will use the assumption of independence of concentration, and so will be written in terms of population density $n(a, \alpha; t)$.

We define a function $\Psi(a, \alpha, \alpha'; t)$ which measures the rate of physiological growth in a time interval dt. More precisely $\Psi(a, \alpha, \alpha', t)\, da'$ will be the rate at time t of transitions $\alpha \to (\alpha + \alpha', \alpha + \alpha' + d\alpha')$ conditional on a chronological age a. By convention we will assume that α' is positive although there are phenomena such as recovery from radiation damage that might require negative α' for their description (Elkind and Sutton, 1960). The transition rate at time t from age α will be denoted by $\Phi(a, \alpha, t)$ and by definition is

$$\Phi(a, \alpha, t) = \int_0^\infty \Psi(a, \alpha, \alpha', t)\, d\alpha'. \tag{2}$$

This rate will always be assumed finite. The rate at which organisms die at time t will be denoted by $\lambda(a, \alpha, t)$. At this point we can write the fundamental equation for $n(a, \alpha; t)$ as

$$\begin{aligned} n(a, \alpha; t) = {} & n(a - dt, \alpha; t - dt)[1 - \Phi(a, \alpha, t)\, dt] \\ & + \int_0^\alpha n(a - dt, \alpha - \alpha', t - dt)\, \Psi(a - dt, \alpha - \alpha', \alpha', t - dt)\, d\alpha'\, dt \\ & - \lambda(a, \alpha, t)\, n(a, \alpha; t)\, dt. \end{aligned} \tag{3}$$

The first term on the right describes organisms whose physiological age does not grow in $(t, t + dt)$; the second describes organisms whose physiological age does advance in $(t, t + dt)$, while the third describes the removal of organisms by death. Terms representing immigration or emigration can be added in an obvious way.

If we expand equation (3) around a and t and retain first order terms in dt, we find that n satisfies

$$\frac{\partial n}{\partial t} + \frac{\partial n}{\partial a} = -(\lambda + \Phi)n + \int_0^\alpha n(a, \alpha - \alpha', t)\, \Psi(a, \alpha - \alpha', \alpha', t)\, d\alpha' \qquad (4)$$

which is a generalization of the von Foerster equation. A modified form of this equation must be supplemented by boundary conditions which describe the production of new cells by mitosis if this is part of the system being described. As an example, let us consider the case of binary fission. For simplicity we will assume that newborn cells are characterized by a physiological age $\alpha = 0$. We now define a rate of reproduction of daughter cells by cells with parameters a and α, calling this rate $\rho(a, \alpha, t)$. The number of newborn cells at time t will be denoted by $n(0, 0, t)$, and satisfies†

$$n(0, 0; t) = 2 \int\int n(a, \alpha; t)\, \rho(a, \alpha, t)\, da\, d\alpha. \qquad (5)$$

In addition to specifying this boundary condition, we must also modify equation (4), since cells disappear from an infinitesimal (a, α) rectangle by fission as well as by death or changes in α. The modified equation can be written

$$\frac{\partial n}{\partial t} + \frac{\partial n}{\partial a} = -(\lambda + \Phi + \rho)n + \int_0^\alpha n(a, \alpha - \alpha', t)\Psi(a, \alpha - \alpha', \alpha', t)\, d\alpha'. \qquad (6)$$

Approximate Equations. It is impossible to write a solution in closed form to equations (4) or (6) as it is in the case of the von Foerster equation. However, it is possible to derive approximations to these equations which are themselves much easier to deal with. The first of these is the Fokker-Planck approximation in which it is essentially assumed that the increment in physiological age is small, in a sense to be specified more exactly below, in the time interval $(t, t + dt)$. The second approximation is one in which α is taken to be a discrete variable.

Let us first consider the Fokker-Planck approximation. With the notation

$$\mu_n(a, \alpha; t) = \int_0^\infty (\alpha')^n\, \Psi(a, \alpha, \alpha', t)\, d\alpha' \qquad (7)$$

† Notice that the number of cells with chronological age between 0 and dt at time t is $n(0, 0, t)dt$ so that, for this special value of a, n has the dimension (time)$^{-1}$ rather than (time)$^{-2}$.

we make the following assumptions:

1. $\mu_1, \mu_2 < \infty$
2. $\mu_j = 0$ for $j \geq 3$
3. $\Psi(a, \alpha, \alpha', t)$ is analytic in α for all a, α' and t
4. $n(a, \alpha; t)$ is analytic in α for all a and t.

Notice that $\mu_n(a, \alpha, t)$ is the n'th moment of the increase in physiological age in $(t, t + dt)$. The assumptions given above are sufficient to deserve the Fokker-Planck equation from a master equation.‡ In order to derive the Fokker-Planck approximation, we note first of all that the range of integration appearing in equation (6) can be extended from $(0, \alpha)$ to $(0, \infty)$, with the proviso that $n(a, \alpha; t) \equiv 0$ for $a < 0$. With this change made, we expand the integral term in equation (7) in the following manner:

$$\int_0^\infty n(a, \alpha - \alpha', \alpha'; t)\, \Psi(a, \alpha - \alpha', \alpha', t)\, d\alpha'$$

$$= \int_0^\infty \left\{ n(a, \alpha; t) - \alpha' \frac{\partial n}{\partial \alpha} + \frac{(\alpha')^2}{2} \frac{\partial^2 n}{\partial \alpha^2} \cdots \right\} \times$$

$$\left\{ \Psi(a, \alpha, \alpha'; t) - \alpha' \frac{\partial \Psi(a, \alpha, \alpha'; t)}{\partial \alpha} + \frac{(\alpha')^2}{2} \frac{\partial^2 \Psi}{\partial \alpha^2}(a, \alpha, \alpha', t) - \cdots \right\} d\alpha'$$

$$= \Phi n - \frac{\partial}{\partial \alpha}(\mu_1 n) + \frac{1}{2} \frac{\partial^2}{\partial \alpha^2}(\mu_2 n) \tag{8}$$

where we have made use of assumptions 1 and 2 above to drop terms containing μ_j for $j \geq 3$. Thus, in this approximation, equation (4) can be replaced by

$$\frac{\partial n}{\partial t} + \frac{\partial n}{\partial a} = -\lambda n - \frac{\partial}{\partial a}(\mu_1 n) + \tfrac{1}{2} \frac{\partial^2}{\partial \alpha^2}(\mu_2 n). \tag{9}$$

The particular model discussed by Stuart and Merkle is characterized by $\lambda = 0$, $\mu_2 =$ constant. They did not discuss the dependence of n on chronological age, although it is not difficult to do so when mitosis is not involved, that is, when one simply follows a cohort from birth to death. An equation analogous to equation (9) with $\mu_2 = 0$ appears in the work of Bell and Anderson. Their equation includes the depletion by reproduction term—ρn on the right-hand side.

When the physiological age of an organism can be characterized by an integer, as in the Szilard model, it is possible to derive a set of equations analogous to equation (6) by the same type of argument. Let $n(a, r, t)$ be the

‡ Parenthetically it might appear that assumptions 1 and 2 might be generalized to allow a cutoff at $j > 2$. That this does not lead to sensible results is shown in a recent paper by Pawula.

number density of organisms of chronological age at time t, with the number of defects, or equivalently, the physiological age, equal to r. Let $\omega_r(a, t)$ be the rate per cell at which defects are accumulated at time t, given a chronological age a and the presence of r defects; let $\lambda_r(a, t)$ be the death rate per cell under the same conditions. Then a derivation similar to that indicated in equation (3) suffices to establish the set of equations:

$$\frac{\partial n(a, 0, t)}{\partial t} + \frac{\partial n(a, 0, t)}{\partial a} = (\omega_0 + \lambda_0)n(a, 0, t)$$

$$\frac{\partial n(a, r, t)}{\partial t} + \frac{\partial n(a, r, t)}{\partial a} = -(\omega_r + \lambda_r)n(a, r, t) + \omega_{r-1}n(a, r - 1, t) r \geq 1. \quad (10)$$

These equations are valid under the assumption that defects are accumulated singly. When mitosis is an important feature these equations must be modified to take it into account. Let the rate of reproduction per cell with physiological age r be denoted by ρ_r. Then equation (10) is to be replaced by

$$\frac{\partial n(a, 0, t)}{\partial t} + \frac{\partial n(a, 0, t)}{\partial a} = -(\omega_0 + \lambda_0 + \rho_0)n(a, 0, t)$$

$$\frac{\partial n(a, r, t)}{\partial t} + \frac{\partial n(a, r, t)}{\partial a}$$

$$= -(\omega_r + \lambda_r + \rho_r)n(a, r, t) + \omega_{r-1}n(a, r - 1, t) r \geq 1 \quad (11)$$

analogous to equation (6). These hold under the assumption that $a \neq 0$. The production of cells with physiological age equal to zero is described by the boundary condition

$$n(0, 0; t) = 2 \sum_r \int n(a, r; t)\rho_r(a, t)\, da. \quad (12)$$

A general solution to the equations just derived would seem to be out of the question. However, the examination of a simple case is quite instructive. For simplicity we consider a situation in which the physiological age is measured in discrete units. The two assumptions which specify the model are:

1. The rate at which defects are acquired (or that the physiological age advances) is μ per unit time where μ is a constant.
2. The rate at which cells die is of the form $\lambda_r = A + Br$ where A and B are constants, that is, it is proportional to the physiological age.

We will assume that the cells do not reproduce themselves, hence we will

simply follow a cohort of cells from birth to death. The equations characterizing the model are

$$\frac{\partial n(a, 0, t)}{\partial a} + \frac{\partial n(a, 0, t)}{\partial t} = -(A + \mu)n(a, 0, t)$$

$$\frac{\partial n(a, r, t)}{\partial a} + \frac{\partial n(a, r, t)}{\partial t} = \mu n(a, r - 1, t) - (\mu + A + Br)n(a, r, t) r \geq 1. \quad (13)$$

In order to solve this set of equations we introduce a generating function

$$\nu(a, z, t) = \sum_{r=0}^{\infty} n(a, r, t)z^r. \quad (14)$$

This generating function is the solution to

$$\frac{\partial \nu}{\partial a} + \frac{\partial \nu}{\partial t} = (\mu z - \mu - A)\nu - Bz\frac{\partial \nu}{\partial z} \quad (15)$$

subject to an initially specified $\nu(a, z, 0)$. Application of the standard method for solving first order partial differential equations (Duff, 1956) leads to the relation

$$\nu(a, z, t) = e^{(\mu/B)z(1-e^{-Bt})} e^{-(\mu+A)t}\nu(a - t, ze^{-Bt}, 0). \quad (16)$$

In order to follow the development of a cohort of cells, we will assume that a just-born cell ($a = 0$) has a physiological age equal to zero as well. In mathematical terms this condition can be written

$$n(a, r, 0) = N_0\delta(a)\delta_{r,0} \quad (17)$$

where $\delta(a)$ is a Dirac delta function, $\delta_{r,0}$ is a Kronecker delta, and N_0 is the initial number of cells. Thus, $\nu(a, z, 0)$ is

$$\nu(a, z, 0) = N_0\delta(a). \quad (18)$$

From this and equation (16) it follows that

$$n(a, r, t) = \frac{N_0 e^{-(\mu+A)t}}{r!}\left(\frac{\mu}{B}\right)^r (1 - e^{-Bt})^r\delta(a - t). \quad (19)$$

The delta function indicates that for this population, in which no mitosis occurs, the chronological age is equal to the time. The average physiological age can easily be calculated from the generating function and is found to be

$$\bar{r}(a, t) = \sum_{r=0}^{\infty} r\, n(a, r, t) = N_0\frac{\mu}{B}(1 - e^{-Bt}) \exp\left[-(\mu + A)t + \frac{\mu}{B}(1 - e^{-Bt})\right]\delta(a - t). \quad (20)$$

When $A = B = 0$, that is, no deaths occur, this expression reduces to

$$\bar{r}(a, t) = N_0 \mu t \, \delta(a - t) \tag{21}$$

In this case the mean physiological age is proportional to biological age, although there is variation around the mean as indicated by the Poisson distribution for the $n(a, r, t)$:

$$n(a, r, t) = N_0 \frac{e^{-\mu t}}{r!} (\mu t)^r \, \delta(a - t). \tag{22}$$

The parameter $\bar{r}$ in equation (20) is 0 at $t = 0$ and $t = \infty$ and reaches a single maximum. While a decline in mean physiological age with time might seem paradoxical, the explanation is a simple one; the cells that survive the longest tend to be those with the lowest physiological age. Similar results can be obtained for a particular model to be used to solve equation (4). This model is specified by

$$\lambda = A + B\alpha, \Psi = W_0 \exp(-\beta\alpha') \tag{23}$$

where A, B and W_0 are constants. For this case the Laplace transform with respect to α plays the same role as the generating function for the solution of equation (13). Since no new qualitative information emerges from the analysis, we will not present the results here.

The preceding results for a scalar physiological age are easily generalized, at least formally, to yield equations valid for the case of a multivariate physiological age. In view of the fact that data to support such a model are not presently available and that the consequences of the present theory are not fully developed, we will not give an account of the more complicated theory at the present time.

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